CPAP as a useful tool in COVID-19 related Acute Hypoxemic Respiratory Failure: Experience from 3 UK Hospitals

Yasser Noeman Ahmed (Yasser.ahmed1@nhs.net)
Mid and South Essex NHS trust

Niranjan Setty
Mid and South Essex NHS Foundation Trust, UK

Ashraf Roshdy
Barts NHS trust

Duncan J Powrie
Mid and South Essex NHS Foundation Trust, UK

Dora A Amran
Mid and South Essex NHS Foundation Trust, UK

Alguili Elsheikh
Mid and South Essex NHS Foundation Trust, UK

Sriya Gokaraju
Mid and South Essex NHS Foundation Trust, UK

Anne Tear
Mid and South Essex NHS Foundation Trust, UK

Maryam Noeman
Medical Student, University College London, UK

Maria Darda
Mid and South Essex NHS Foundation Trust, UK

Iman El Sayed
Medical Research Institute, Alexandria University, Alexandria, Egypt

Vijayalakshmi Karunanithi
Mid and South Essex NHS Foundation Trust, UK

Mahalingam Aarani
Mid and South Essex NHS Foundation Trust, UK

Muhammad Shafiq
Mid and South Essex NHS Foundation Trust, UK

Abdul-Khaliq
Mid and South Essex NHS Foundation Trust, UK

Johnson Samuel

Mid and South Essex NHS Foundation Trust, UK

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Abstract

Introduction: Severe acute hypoxemic respiratory failure (AHRF) in COVID-19 pneumonia is associated with a high mortality rate, resulting in mounting pressures on intensive care units worldwide. Different oxygenation management protocols are used in different centres. Most centres switch patients who fail to oxygenate adequately using conventional oxygen therapy (COT) methods to non-invasive positive pressure ventilation (NIPPV), usually continuous positive airway pressure (CPAP). Other centres resort to invasive mechanical ventilation (IMV) directly, without a trial of NIPPV. In this trial, we aim to compare the efficacy of different approaches in managing COVID-related AHRF, and ascertain if CPAP therapy reduces the need for IMV.

Methods: We carried out a retrospective cohort study on patients with laboratory-confirmed COVID-19 at three university hospitals in Essex, United Kingdom. We included all patients with significant AHRF (defined as needing oxygen therapy FiO_2 more than 0.4 to maintain an oxygen saturation of 92%) who were deemed eligible for IMV escalation during a 3-month period (1st March to 31st May 2020).

Results: Out of 174 patients who met the criteria, 84 patients received CPAP (Group 1). Half needed intubation (n=42). 90 patients did not have a CPAP trial (Group 2). 76.6% needed intubation (n=69). No difference was found between the two groups in demographic criteria or disease severity. Our results show a significant difference in 60-day mortality between group 1 and 2 (25% versus 37.8%, p=0.02). COT as standalone therapy for COVID-19 patients (group 2) was associated with a trend of more increased risk of intubation and an increased relative risk of death (RR 2.14, 95% CI 1.39 to 3.29). This corresponds to a number needed to treat (NNT) of 3.74 (95% CI 2.47 to 7.73). Patients in group 1 who failed CPAP trial and required intubation did not have an increased risk of mortality when compared to group 2 patients who required intubation.

Conclusion: Our results support introducing CPAP rather than escalating FiO2 in cases refractory to COT. Our study suggests CPAP can be safely used to treat patients with AHRF. Clinical trials are needed to guide recommendations for optimum timing and selection of patients most likely to benefit.

Key Messages

What is the key question?

Would CPAP therapy provide any extra benefit when given to COVID 19 severely hypoxemic patients rather than escalating FiO2 using the conventional oxygen therapy?

What is the bottom line?

CPAP reduced need for intubation and reduced mortality when given early to COVID 19 severely hypoxemic patients even in patients who subsequently needed intubation after prolonged CPAP therapy

Why read on?

COVID 19 pneumonia represents a challenging disease, where the role of CPAP needs more clarifications. This paper represent a huge experience gained during the first wave of COVID 19 pandemic across 3 UK hospitals which could add to our understanding and management plans of CPAP therapy in such patients.

Introduction

The COVID-19 pandemic has caused a huge rise in patients presenting with Acute Hypoxemic Respiratory Failure (AHRF) and mounting pressures on the Intensive Care Units (ICU) across the globe. There is a significant surge in reports from around the world, describing different oxygenation management protocols in different centres. However, there is still variation in the management of COVID-19 related AHRF as evidence by the heterogeneity of protocols in different centres, even within the same country. Most centres switch patients who fail to oxygenate adequately using conventional oxygen therapy (COT) methods (e.g. Venturi Mask or Non Rebreathing Mask (NRM)) to Non-Invasive Positive Pressure Ventilation (NIPPV) usually Continuous Positive Airway Pressure (CPAP), High flow nasal Oxygen (HFNO), or in the minority of patients with CO_2 retention, Bi Level Positive Airway Pressure (BiPAP). Other centres resort to Invasive Mechanical Ventilation (IMV) directly without a trial of NIPPV. Reducing the risk of Aerosol Generated Procedures (AGP) related infection is one of the reasoning behind the latter approach. Marini and Gattinoni strongly support early IMV to avoid progression of the mild disease to a more severe lung injury secondary to the spontaneous vigorous inspiratory efforts leading to patient self-induced lung injury (P-SILI). (1) Others argued that P-SILI should not be used as a justification for pre-emptive IMV, with all its documented complications, without giving the patient a trial of CPAP / BiPAP. (2)

The timing of the endotracheal intubation (ETI) and the location for initiation of IMV vary widely. While some centres will have their severely hypoxemic patients moved to ICU, in others patients are intubated in wards prior to being moved to the ICU. Increasingly, new data to support the use of CPAP/ BiPAP prior to initiation of IMV is being published.

We present in this retrospective study the data collected from three University Hospitals in Essex, United Kingdom comparing different approaches of management of COVID related AHRF. Our aim was to ascertain if CPAP therapy would reduce the need for ETI.

Methods

Inclusion criteria: All adult patients (≥18 years) with confirmed laboratory COVID-19 and significant AHRF defined as needing oxygen therapy (FiO_2 more than 0.4) to maintain an oxygen saturation of 92%, and who were deemed eligible for escalation for IMV during a 3-month period (1st of March to 31st of May 2020) from three University hospitals in UK. Patient data and outcomes were retrospectively extracted from patient records.

Data were collected retrospectively and anonymously and no patient consent was required.

Exclusion Criteria: Patients with limits of care which included do not intubate (DNI) order as per the treating physician.

Statistical analysis: Qualitative and quantitative variables were summarized with frequencies (absolute and relative, percentage) and central tendency (means and medians) and variability (standard deviations, SD, and interquartile ranges, IQR) indicators, depending on their parametric distribution. Student t test as well as Chi-Square test were used for quantitative and qualitative variables. Kaplan-Meier survival analysis using Log rank test compared 60-days mortality between the CPAP versus non-CPAP groups using R software **("survminer" package).**

Results

Patients requiring CPAP were treated in either negative pressure or rooms with adequate air changes with non-invasive monitoring. Health care workers caring for patients used full personal protective equipment (PPE) as per Public Health England advice. Non vented masks were used. All patients were treated in the respiratory wards (acute respiratory care areas) and managed by the respiratory medical and nursing team with input from the critical care outreach team. CPAP was initiated at pressures of 5-8 cm H_2O and increased up to 10-12 cm H_2O depending on patient comfort and treatment response. In one of the three sites in the trust, CPAP was not used and patients who did not respond were triaged to IMV directly.

174 patients met the above inclusion criteria. They were subsequently divided into two groups:

Group 1: Patients who received CPAP treatment (n=84)

Group 2: Patients who did not have a CPAP trial (n=90)

Clinical details and outcomes are shown in table 1. The outcome of the whole cohort of patients is shown in figure 1. There was a significant 60-days mortality difference between group 1 and 2 (25% versus 37.8%, p=0.02). Twenty-one patients in group 1 died, including one before invasive mechanical ventilation after suffering a pulmonary embolism.

Table 1: Characteristics of the 2 groups of patients

	Cohort (n=174)			
	Total	**Group 1** (n=84)	**Group 2** (n=90)	**p-value**
Demographics n(%)				
Age (mean± SD)	59.3±12.3	59.6±11.1	59.1±13.3	.805
Male (%)	128 (73.5%)	58(69%)	70(77.7%)	.057
Co-morbidities (%)				
• Hypertension	77 (44.3%)	36(42.9%)	41(45.6%)	.720
• Diabetes Mellitus	41 (23.6%)	24(28.6%)	17(18.9%)	.133
• Ischemic heart disease	41 (23.6%)	16(19%)	25(27.8%)	.668
• Malignancy	7 (4%)	3(3.6%)	4(4.4%)	1
• CKD	8 (4.5%)	6(8.5%)	2(3.4%)	.294
• COPD	43(24.7%)	22(26.2%)	21(23.3%)	.662
• No co-morbid illness	75(43.1%)	41(48.8%)	34(37.8%)	.142
Baseline respiratory variables (mean±SD)				
SaO_2 (%)	93.8 ±4	93.7±3.8	94.0±4.5	.746
PaO_2 (kPa)	10.29±5.61	10.14(4.42)	10.62(7.62)	.671
FiO_2	74.5±26.1	68.8±25.9	86.9±22.0	<.001*
P/F ratio	113 ±63	118.5±55.5	101.2±76.1	.170
S/F ratio	140 ±49	142.2±51	135 ±44	.483
Outcome				
Total duration on oxygen therapy (hours)	52.6±71.4	37.6±44.7	74.4±94.2	.007*
Intubation (n,%)	111 (63.8)	42 (50)	69 (76.6)	.866
Mortality after ETI (n,% of intubated patients)	54 (31.0)	20 (48)	34 (49.2)	.07

Overall Mortality (n,%)	55 (31.6)	21 (25)	34 (37.8)	.02*
Total LoS	16.8±14.9	18.0±13.2	15.7±16.3	.315

Data are presented as n (%) or mean±SD, unless otherwise stated. Statistical significance at $p<0.05$; *Significant results, COPD: chronic obstructive pulmonary disease, CKD: Chronic kidney disease, LoS: Length of stay.

Discussion

In this retrospective study, we compared COVID-19 patients who had CPAP prior to IMV with those who were directly treated with IMV after receiving only conventional oxygen therapy (COT). Mortality in patients who were invasively ventilated was not different in both groups (Table 1). However, the overall mortality was significantly less in the CPAP group (25% vs 37.8%, p=0.02). There was no baseline difference in the patient demographics and severity of illness. Our analysis shows that COT as standalone therapy for COVID-19 patients (group 2) was associated with a trend of more intubation a relative risk of death of 2.14 which was statistically significant (95 % CI 1.39 to 3.29). This corresponds to a number needed to expose (NNE) of 3.74 (95% CI 2.47 to 7.73) (i.e. 4 patients would have to receive CPAP (instead of only oxygen therapy) to reduce mortality by one).

CPAP trial failure is not associated with increased mortality when compared to patients who needed ETI without a CPAP trial as the mortality in both these groups who went on to have IMV was similar (Table 1). Our study though small, suggests CPAP can be safely used to treat patients with AHRF and adds to a number of studies recently published with similar results. An Italian group was able to show in a prospective multicentric work (n=157) that helmet CPAP can help to avoid intubation in nearly half of COVID-19 patients (27). A single centre before-after French study (n=52) showed CPAP to be significantly associated with reduced need for intubation in COVID-19 patients (11).

Our results support introducing CPAP rather than escalating FiO_2 in refractory to COT cases. The exposure to high FiO_2 is known to be associated with harm in the form of impaired lung function and resorption atelectasis (22). Some subgroup of patients can benefit from CPAP and avoid ETI with all its associated adverse effects.

Frat et al compared NIV to COT and HFNO in AHRF and concluded no difference in the rate of ETI (13). The underlying mechanism can be the lung injurious vigorous spontaneous breathing, a phenomenon known as P-SILI (patient self-inflicted lung injury). P-SILI is more probable when a vigorous respiratory effort is superimposed on severe ARDS adding insult to injury (9). On the other hand, an increase in transpulmonary pressure and tidal volume after CPAP can theoretically lead to a higher regional lung stress and strain especially in non-homogenous ARDS lungs (10). To note that both P-SILI and diaphragmatic injury are possible after prolonged and strenuous breathing even without any respiratory support (e.g. CPAP) (8,10). In fact, considering atelectasis as a risk factor for P-SILI, lung recruitment by

CPAP, better oxygenation (hence reduced hypoxic drive) and more homogenous distribution of ventilation may reduce the risk of P-SILI in CPAP treated patients. (8,14,15)

The added risk of infection transmission boosted the early views leaning to avoid CPAP in COVID-19 patients. While It is difficult to confirm the risk associated with every AGP, the role of NIV remains without strong evidence (16). The distance of droplet transmission is flow dependent and can be greater with CPAP masks. However, even Oxygen face masks can be associated with infection transmission (16-18). HFNO associated risk is less clear but considering its high flow rates it can be associated with significant risk. One Italian group, and despite PPE, showed that 11% of the staff caring for COVID-19 patients in respiratory units acquired COVID-19 (30). In general, healthcare workers (HCWs) constitute 3.8-10% of COVID-19 patients (16,24). Paradoxically, CPAP can counterbalance its harm by avoiding ETI which is one of the most established AGP (16).

In our observation in patients showing less respiratory distress and appropriate respiratory drive may be less liable to P-SILI and can benefit most from CPAP. Gattinoni et al described CARDS phenotypes including patients presenting with nearly normal lung compliance which means the need for less CPAP pressure (25).

In the middle of such strain on critical care resources, we can show the successful application of CPAP out of the ICU by respiratory teams in dedicated pulmonary units, a finding confirmed earlier by Oranger and Franco et al (11,30). With the increased strain on ICU resources during the COVID-19 surge, CPAP and NIV became successfully used as a bridge either to recovery or ETI (5-7). CPAP therapy can help save both ICU and wards resources by a combination of its applicability pre-ICU, avoiding ETI and overall shorter LOS. However, the early detection of the subgroup of patients indicated for ETI remains the mostly challenging when managing AHRF in COVID-19 patients.

Our studies have many limitations: It is a retrospective small sample study and not randomised. However, we think it can add along with other works to the cumulative knowledge about CARDS. We mainly used one CPAP interface (face mask) and cannot report on others especially Helmet which showed benefit in other works (26,27). Our work shows that CPAP trial is warranted in COVID-19 patients presenting with AHRF under close monitoring. This trial can be safely applied in out of ICU respiratory units by a trained team.

We also believe that CPAP could be a valuable tool in low resourced settings and also it is included in WHO COVID 19 clinical guidance (28). Clinical trials are needed to guide recommendations for optimum timing and selection of patients who most likely to benefit.

We still await the results of randomised control trial to compare CPAP, HFNO and standard oxygen or the IMV (29). Until such robust data are published, our observation suggest that CPAP has a role in management of type 1 respiratory failure due to COVID 19.

Declarations

Conflict of Interest

Authors document no conflict of interest.

Ethics

The study is registered and approved under the registration numbers 20007, date 20/03/2020 Mid and South Essex Hospitals NHS trust. Patients consent waived as retrospective anonymous data.

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Figures

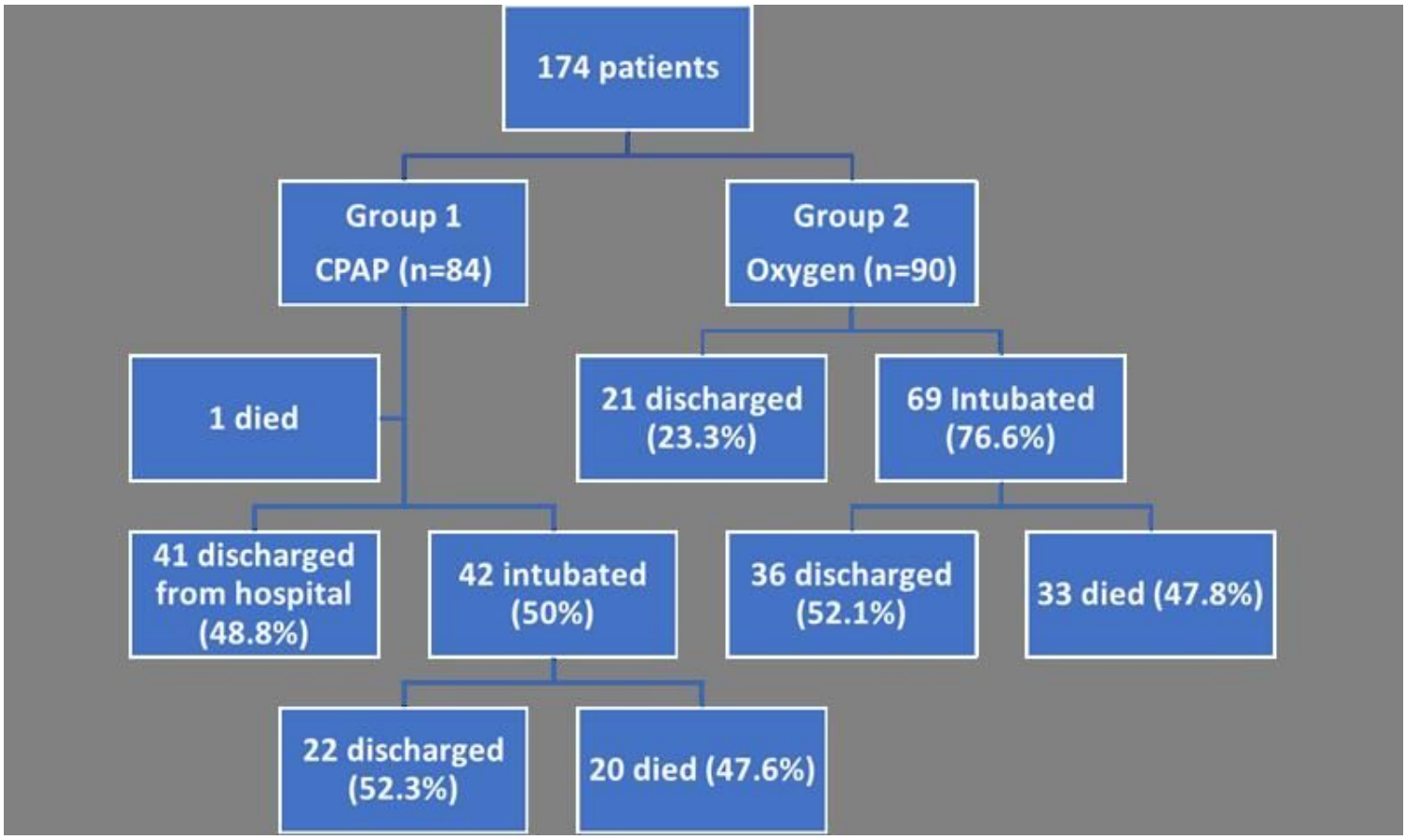

Figure 1

Outcome of the 2 studied groups

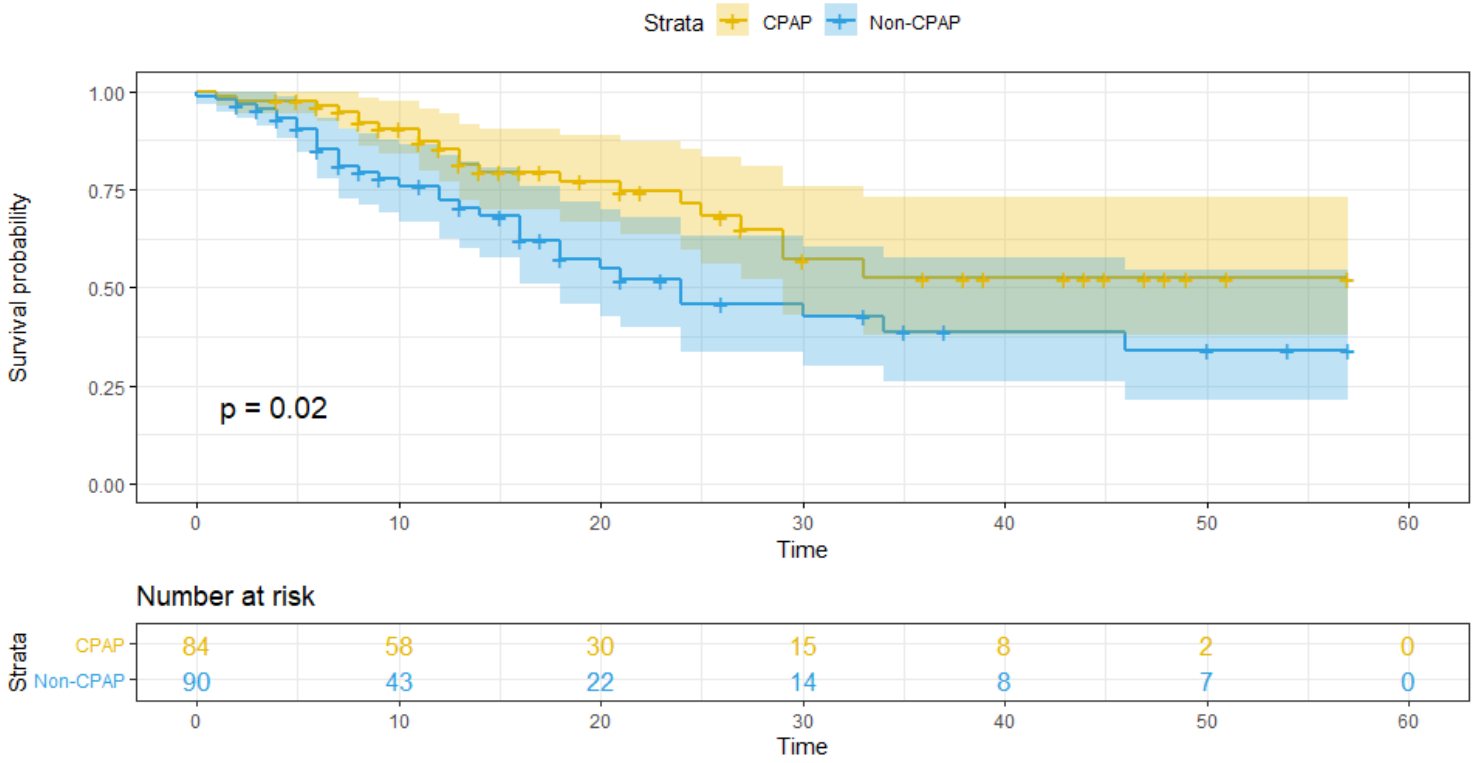

Figure 2

Kaplan Meier curve showing 60 days mortality for the 2 studied groups 60-days cumulative proportion surviving is 52.4% for patients on CPAP Compared to 33.9% for patients on Oxygen, Log Rank (Mantel-Cox) X2=5.38, p=.020